Cinacalcet for secondary hyperparathyroidism in ESRD patients on dialysis

The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end-stage renal disease patients on dialysis: a systematic review and economic evaluation

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Executive summary

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Executive summary

Background

The parathyroids are four small glands found in the neck, close to the thyroid. Normally, homeostatic control of serum calcium and phosphate levels is regulated within narrow bounds through parathyroid hormone (PTH) released by the parathyroids. Secondary hyperparathyroidism (SHPT) is a common complication of end-stage renal disease (ESRD). It may develop early in chronic kidney disease (CKD) and progresses as renal function deteriorates. As it does so, the combined effects of reduced serum calcium, increased serum phosphate and decreased vitamin D activity lead to overactivity of the parathyroid glands as they try to maintain appropriate calcium levels. Eventually, the parathyroids may develop reduced expression of calcium and vitamin D receptors and so are less responsive to changes in serum levels that they should regulate.

There is an increased risk of vascular disease due to calcification in SHPT. SHPT is also the main cause of renal bone disease, which increases the risk of fracture. The relative impacts of calcium, phosphate and PTH, being complex, are unclear. Symptomatically, advanced SHPT can cause bone pain, muscle weakness and itching.

Current standard treatment for SHPT is based on reducing phosphate in the diet, use of phosphate binders (which contain calcium), vitamin D supplements and parathyroidectomy (surgical removal of the parathyroids). Currently, the Renal Registry reports that 72% of people meet target levels for PTH, 60% for phosphate and 63% for calcium.

Cinacalcet (Mimpara®; Amgen, Thousand Oaks, California, USA) is the first of a new class of calcimimetic drugs, which acts directly on parathyroid calcium receptors to increase their sensitivity to serum calcium. This suppresses overproduction of PTH which, in turn, reduces elevated serum calcium and phosphate levels.

Objectives

To establish the effectiveness and cost-effectiveness of cinacalcet for the treatment of SHPT for people on dialysis due to ESRD.

Methods

Systematic review

Electronic databases were searched for relevant published literature on the clinical effectiveness of cinacalcet for SHPT in ESRD. Updated searches were undertaken in February 2006. Included randomised controlled trials (RCTs) were critically appraised for internal and external validity. Relevant data were extracted and, as the largest trials were already pooled using patient-level data, a narrative synthesis was carried out.

Cost-effectiveness

Electronic databases were searched for relevant published literature on the cost-effectiveness of cinacalcet for SHPT in ESRD. No studies were identified. An economic evaluation was submitted by Amgen, the manufacturers of cinacalcet, to the National Institute for Health and Clinical Excellence as part of its appraisal of cinacalcet. This was critically appraised and compared with the authors' economic evaluation.

A Markov (state-transition) model was developed by the authors. The model compared cinacalcet in addition to current standard treatment with phosphate binders and vitamin D to standard treatment alone. A simulated cohort of 1000 people aged 55 years with SHPT was modelled until the whole cohort was dead. Incremental costs and quality-adjusted life-years (QALYs) were calculated. Extensive one-way sensitivity analysis was undertaken as well as probabilistic sensitivity analysis.

Results

Number and quality of studies

Seven published reports of RCTs comparing cinacalcet plus standard treatment to placebo plus standard treatment were identified. However, most of these papers related to just four Amgen trials which were more fully reported, including providing pooled data, in the medical review of cinacalcet by the US Food and Drug Administration. Therefore, this review was based on these four Amgen trials plus the three published papers that report on different trials. ▶

Details from a total of seven trials were therefore included in the systematic review, including a total of 846 people randomised to receive cinacalcet.

The trials were largely well designed. The primary outcome for all the trials was a measure of serum PTH reduction. Only one paper provided information about patient-based clinical outcomes. This used retrospective analysis of adverse effect data from the four main RCTs to assess the impact of cinacalcet on fracture, cardiovascular events, parathyroidectomy and mortality. However, most of these data were based on 6-month follow-up and it is unclear how the results should be extrapolated to the longer term. Some data came from people who agreed to take part in an extension study after the original 6-month deadline and it is not known whether their characteristics were the same as the originally randomised population. Methods used for censoring in the analysis were unclear. In addition, death rates in the trials were half that reported for a similar age group by the UK Renal Registry. It is therefore unclear whether the results are applicable to the routine clinical population.

Summary of risks and benefits

Cinacalcet in addition to standard treatment was more effective at meeting PTH target levels than placebo plus standard treatment (40% versus 5% in pooled analysis, $p < 0.001$). Of those patients meeting PTH targets, 90% also experienced a reduction in calcium–phosphate product levels compared with just 1% of those treated with placebo. Cinacalcet was more effective among those with moderately elevated PTH levels than those with very high levels of PTH, but in all cases was more effective than standard treatment at reaching target PTH levels (baseline PTH levels >32 to <53 pmol/l 60% versus 11%, >53 to <85 pmol/l 41% versus 2%, >85 pmol/l 12% versus 0).

One paper reported patient-based clinical outcomes using pooled adverse effect data from four RCTs. Significantly fewer people treated with cinacalcet were hospitalised for cardiovascular events [15.0 versus 19.7 cardiovascular events per 100 patient-years, relative risk (RR) 0.61, $p = 0.005$], although no difference was seen in all-cause hospitalisation or mortality. Significantly fewer fractures (3.2 versus 6.9 events per 100 patient-years, RR 0.46, $p = 0.04$) and parathyroidectomies (0.3 versus 4.1 events per 100 patient-years, RR = 0.07, $p = 0.00$) were also seen with cinacalcet, although these findings are based on small numbers. Given the short follow-up, it is not clear to what extent these results can be extrapolated to the longer term.

Withdrawal due to adverse effects was more common for those treated with cinacalcet than for those treated with placebo (15% versus 8%). Pooled incidence of serious adverse effects was not different between the study arms. However, there was significantly more nausea (31% versus 19%, $p < 0.001$) and vomiting (27% versus 15%, $p < 0.001$) among those treated with cinacalcet. Vomiting was related to the dose of cinacalcet received.

Summary of costs

The authors' cost–utility model estimates that the lifetime cost of standard treatment for SHPT is £6533 for a person with ESRD aged 55 years. The additional cost of cinacalcet is estimated at £21,167 (about £3800 annually). If the costs of dialysis are included in this assessment, standard care costs £81,523 and cinacalcet adds £25,423.

Summary of cost-effectiveness

Amgen submitted an estimate of cost–utility based on a Markov (state-transition) model, using data from the research report assessing the impact of cinacalcet on cardiovascular events, fractures, parathyroidectomies and mortality. This estimates the discounted incremental cost-effectiveness ratio (ICER) for cinacalcet in addition to standard care compared with standard care alone for people with SHPT as £35,600 per QALY.

The authors' model estimates that, compared with standard treatment alone, cinacalcet in addition to standard care costs an additional £21,167 and confers 0.34 QALYs (or 18 quality-adjusted weeks) per person. The ICER is £61,890 per QALY.

Analyses of uncertainty

One-way sensitivity analysis suggested that the model was particularly sensitive to a number of transition, utility and cost parameters. These were further investigated through threshold analyses. In most cases, even extreme adjustments to individual parameters did not result in an ICER below a willingness-to-pay (WTP) threshold of £30,000 per QALY. An ICER of £30,000 per QALY was achieved if the cost of cinacalcet was reduced from 14.5p to 8p per mg. The ICER also fell below £30,000 in one-way threshold analysis if the relative risk of death associated ▶

with having 'very uncontrolled' PTH levels (>85 pmol/l) compared with meeting target levels of 32 pmol/l was raised to 2.2 (compared with 1.1814 in the base case).

In probabilistic analysis only 0.5% of simulations showed cinacalcet to be cost-effective at a WTP threshold of £30,000 per QALY. The cost-effectiveness acceptability curve shows that cinacalcet is only likely to be the most cost-effective treatment option above a WTP threshold of £62,000 per QALY.

The cost-effectiveness was evaluated of only treating those with moderately uncontrolled PTH (>32 <85 pmol/l). This reduced the ICER only slightly to £57,422 per QALY. Only treating those with very uncontrolled PTH levels (>85 pmol/l) increased the ICER to £81,479 per QALY.

The impact of altering the assumptions in the model by using different data sources for the inputs was also assessed. The range of ICERs for these analyses was £39,000 to £92,000 per QALY.

Discussion

The systematic review shows that cinacalcet is effective at reducing levels of PTH in people with SHPT. However, the identified studies have short follow-up and it remains unclear whether this impact will be maintained in the long term or what long-term impact will be seen on parathyroidectomy, fracture, cardiovascular events and mortality.

Although there is considerable uncertainty in many of the parameters used in the cost-effectiveness model, extensive sensitivity analysis shows that cinacalcet is unlikely to be considered cost-effective at usually acceptable levels of willingness to pay.

This assessment comprises a comprehensive assessment of the effectiveness and cost-effectiveness of cinacalcet for SHPT by an independent team through systematic review and economic modelling.

Better information about the relative impact of different biomarkers on clinical outcomes would allow a more precise estimation of the impact of cinacalcet. In addition, the assessment has been hampered by the lack of long-term follow-up data for people treated with cinacalcet compared with standard care.

Conclusions

Cinacalcet in addition to standard care is more effective than placebo plus standard care at reducing PTH levels without compromising calcium levels. However, there is limited information about the impact of this reduction on patient-relevant clinical outcomes. Given the short follow-up in the trials, it is unclear how data should be extrapolated to the long term. Together with the high drug cost, this leads to cinacalcet being unlikely to be considered cost-effective.

Recommendations for research

The following topics are recommended for further research.

- Accurate estimates of the multivariate relationship between biochemical disruption in SHPT and long-term clinical outcomes are of paramount importance for future efforts to model the effectiveness of cinacalcet, or other similar agents.
- Longer term studies of the maintenance of PTH control in SHPT and of the clinical impact with cinacalcet are needed. Such studies should explicitly examine the impact of cinacalcet in subgroups based on age and diabetes.
- A better understanding of the epidemiology of fractures in SHPT is needed, including the pattern of fractures experienced in SHPT, and their consequences in terms of health service use, quality of life and mortality.
- The impact of fracture, cardiovascular events and very uncontrolled PTH levels on the quality of life of people with SHPT should be investigated.

Publication

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